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Patients With Early Diabetic Heart Disease Demonstrate a Normal Myocardial Response to Dobutamine

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OBJECTIVES We sought to use quantitative markers of the regional left ventricular (LV) response to stress to infer whether diabetic cardiomyopathy is associated with ischemia.

BACKGROUND Diabetic cardiomyopathy has been identified in clinical and experimental studies, but its cause remains unclear.

METHODS We studied 41 diabetic patients with normal resting LV function and a normal dobutamine echo and 41 control subjects with a low probability of coronary disease. Peak myocardial systolic velocity (Sm) and early diastolic velocity (Em) in each segment were averaged, and mean Sm and Em were compared between diabetic patients and controls and among different stages of dobutamine stress.

RESULTS Both Sm and Em progressively increased from rest to peak dobutamine stress. In the diabetic group, Sm was significantly lower than in control subjects at baseline (4.2 ± 0.9 cm/s vs. 4.7 ± 0.9 cm/s, $p = 0.012$). However, Sm at a low dose (6.0 ± 1.3), before peak (8.4 ± 1.8), and at peak stress (8.9 ± 1.8) in diabetic patients was not significantly different from that of controls (6.3 ± 1.4, 8.9 ± 1.6, and 9.6 ± 2.1 cm/s, respectively). The Em (cm/s) in the diabetic group (rest: 4.2 ± 1.2; low dose: 5.0 ± 1.4; pre-peak: 5.3 ± 1.1; peak: 5.9 ± 1.5) was significantly lower than that of controls (rest: 5.8 ± 1.5; low dose: 6.6 ± 1.5; pre-peak: 6.9 ± 1.3; peak: 7.3 ± 1.7; all $p < 0.001$). However, the absolute and relative increases in Sm or Em from rest to peak stress were similar in diabetic and control groups.

CONCLUSIONS Subtle LV dysfunction is present in diabetic patients without overt cardiac disease. The normal response to stress suggests that ischemia due to small-vessel disease may not be important in early diabetic heart muscle disease. (J Am Coll Cardiol 2003;42:446–53)
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A number of experimental, pathologic, and epidemiologic studies support the existence of diabetic cardiomyopathy (1), the clinical diagnosis of which is made when systolic and diastolic left ventricular (LV) dysfunction are present in diabetic patients without other known cardiac disease (2–4). As with other conditions where new cardiac imaging technologies have identified subclinical heart disease (5–7), myocardial backscatter and strain characteristics in patients with diabetes mellitus have been shown to be abnormal (8,9).

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Diabetic cardiomyopathy may be an important contributor to the susceptibility of diabetic subjects to the development of heart failure and to their worse outcome with this condition (10). As treatment to reverse this disorder is more likely to be effective at an early (preclinical) stage, defining the mechanism of diabetic cardiomyopathy may be important to its selective treatment. However, the etiologic agent for diabetic heart disease remains undefined—the most likely contributors being disturbances of cardiac muscle, pathology involving the cardiac stroma (e.g., fibrosis), or disease of the small vessels. The separation of these etiologies is difficult with standard technologies, and given the asymptomatic status of patients with preclinical disease, a biopsy study would be difficult to justify.

Small-vessel disease is common in diabetic subjects, such that this pathology may merely correlate with diabetic heart disease, perhaps through common mechanisms. If vascular disease were causative, it might be expected that the ventricular response to stress would be abnormal. Tissue Doppler-derived myocardial peak systolic velocity (Sm) and peak early diastolic velocity (Em) are more sensitive indexes of LV systolic and diastolic function than conventional echocardiography and have enabled quantification of systolic and diastolic function at rest and during stress (11,12). We therefore sought to apply tissue Doppler indexes of systolic and diastolic function (Sm and Em) to identify whether patients with diabetic cardiomyopathy had an abnormal stress response, implying an etiologic contribution from small-vessel disease.

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Abbreviations and Acronyms

A = mitral peak late diastolic velocity
BP = blood pressure
CAD = coronary artery disease
DbE = dobutamine stress echocardiogram/echocardiography
E = mitral peak early diastolic velocity
Em = myocardial peak early diastolic velocity
HR = heart rate
LV = left ventricle/ventricular
Sm = myocardial peak systolic velocity
TDI = tissue Doppler imaging

METHODS

Subjects. We studied 41 patients with diabetes mellitus (29 male and 12 female; mean age 59 ± 9 years) and 41 control patients with a low probability of coronary disease (23 male and 18 female; mean age 56 ± 8 years). Subjects were eligible for recruitment if they had an ejection fraction >50% (as assessed by the modified biplane Simpson's method), no history of coronary artery disease (CAD), a normal stress echocardiogram and/or coronary angiogram, and no LV hypertrophy. Subjects were excluded if they had abnormal systolic function, moderate to severe valvular disease, rest or stress wall motion abnormalities, CAD, LV hypertrophy, atrial fibrillation or other severe arrhythmias, or congenital heart disease. The control subjects were considered to have a low probability of coronary disease on clinical grounds and had a normal dobutamine stress echocardiogram (DbE).

Standard echocardiography. Resting echocardiography was performed in the left lateral decubitus position, using a standard commercial ultrasound machine (Vivid 5, GE Vingmed, Horten, Norway) with a 2.5-MHz phased-array probe. Images were obtained in the standard tomographic views of the LV (parasternal long and short axis and apical four-chamber, two-chamber, and long-axis views). Mitral inflow velocities were recorded by using conventional pulsed-wave Doppler echocardiography, positioning a sample volume at the level of the mitral leaflet tips in the apical four-chamber view. The peak early diastolic velocity (E), peak late diastolic velocity (A), E/A ratio, isovolumic relaxation time, and E-wave deceleration time were measured on line. All images were saved digitally in raw-data format to a magneto optical disk (EDM-2300B, Sony Electronic Inc., Saitama, Japan) for offline analysis.

Left ventricular diameters and wall thicknesses were measured from the two-dimensional targeted M-mode echocardiographic tracings in the parasternal long axis, according to the criteria of the American Society of Echocardiography (13). Fractional shortening was calculated by the formula: (end-diastolic LV dimension − end-systolic LV dimension)/end-diastolic LV dimension (14). The LV mass was determined by Devereux's formula: LV mass (g) = 1.04 ([end-diastolic LV dimension + end-diastolic septal thickness + end-diastolic posterior wall thickness]^3 − [end-diastolic LV dimension]^3) − 13.6 (15). Left ventricular hypertrophy was defined as LV mass index >131 g/m^2 in men and >100 g/m^2 in women (16). The LV end-diastolic and end-systolic volumes at rest were computed from two- and four-chamber views, using a modified Simpson's biplane method, and the LV ejection fraction was calculated. Each representative value was obtained from the average of three measurements.

Tissue Doppler imaging and dobutamine stress test. Myocardial velocities were recorded by activating the color tissue Doppler function to record low-velocity, high-intensity myocardial signals at a high frame rate (120 MHz), giving a temporal resolution of 8 ms. Data were acquired in the apical views to assess myocardial long-axis function. The imaging angle was adjusted to ensure a parallel alignment of the beam with the myocardial segment of interest. After recording resting baseline tissue Doppler imaging (TDI), dobutamine was administered using a standard 3-min incremental DbE protocol (5 to 40 μg/kg per min) (17), and TDI was recorded before each increment. Patients who failed to achieve 85% of their maximal age-predicted heart rate (HR) were given 1 mg atropine in increments of 0.25 mg until the target HR was achieved. The 12-lead electrocardiogram (Marquette Case 15, Marquette, Wisconsin) was monitored throughout, and blood pressure (BP) was recorded at rest and at 3-min intervals during infusion and recovery. End points of the stress protocol were completion of the protocol, progressive or severe chest pain, serious ventricular arrhythmia, systolic BP >240 mm Hg, symptomatic hypotension or systolic BP <100 mm Hg, or intolerable side effects. Data were saved in digital format for offline analysis.

Regional wall motion analysis was assessed using a standard 16-segment model (18) of the four tomographic views of the LV by two observers blinded to the patient's clinical and angiographic data. Wall motion was scored as normal, mildly hypokinetic, severely hypokinetic, and akinetic; patients with hypokinesia or akinesia at any stage of a dobutamine stress test were not recruited into the study.

Each of six walls from the three apical views was divided into basal, mid, and apical segments. Using offline analysis software, segmental velocity profiles within a 9 × 9 pixel sample volume were derived at baseline, low dose, pre-peak, and peak stress at the basal aspect of the basal, mid, and apical segments of the septal, lateral, anteroseptal, posterior, inferior, and anterior LV walls from base to apex (Echopac, GE Vingmed, Horten, Norway). Myocardial peak systolic and early diastolic filling velocities in each segment were measured and averaged for each patient at rest and each stage of dobutamine stress (Fig. 1). Thirty-one segments were excluded from the analysis, including segments that were poorly visualized or with a >20° angle between their long axis and the Doppler beam, or with a change of image orientation during stress.

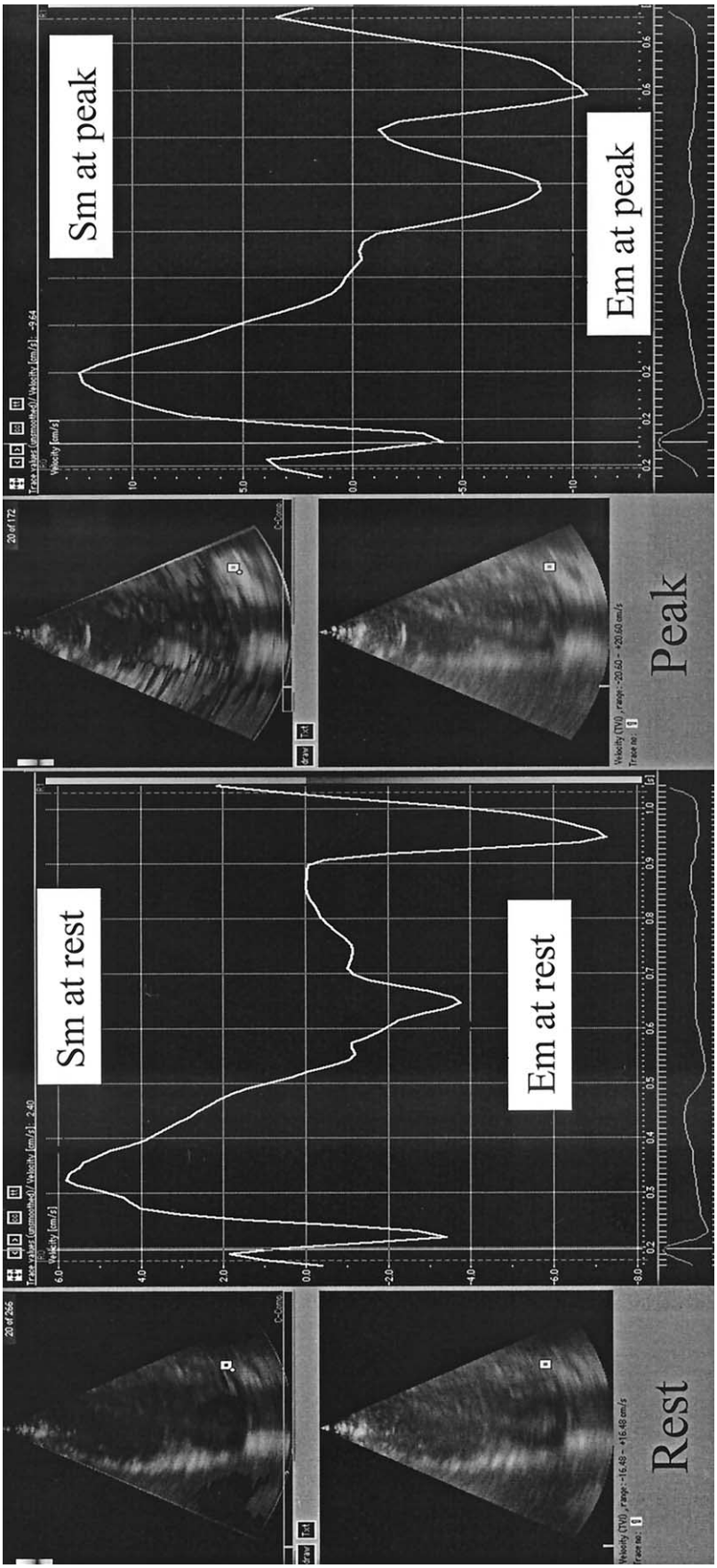

Figure 1. Measurement of myocardial peak systolic velocity (Sm) and myocardial peak early diastolic velocity (Em) at rest (**left**; heart rate 69 beats/min) and at peak (**right**; heart rate 128 beats/min) in a 69-year-old diabetic patient. The Sm at the basal part of the lateral wall at rest and peak were 5.8 and 12.4 cm/s, respectively. The Em at the basal part of the lateral wall at rest and peak were 3.8 and 8.5 cm/s, respectively.

Table 1. Clinical Characteristics of Each Group

	Control Group (n = 41)	DM Group (n = 41)	p Value
Age (yrs)	56 ± 8	59 ± 9	NS
Resting HR (beats/min)	72 ± 13	75 ± 11	NS
Peak HR (beats/min)	143 ± 8	140 ± 11	NS
Resting SBP (mm Hg)	133 ± 23	141 ± 28	NS
Resting DBP (mm Hg)	74 ± 12	76 ± 14	NS
Peak SBP (mm Hg)	170 ± 30	158 ± 38	NS
Peak DBP (mm Hg)	81 ± 14	74 ± 15	0.034
Weight (kg)	76 ± 16	89 ± 21	0.007
Body mass index (kg/m^2)	27 ± 5	30 ± 7	0.01
Hypertension	20/41 (49)	24/41 (59)	NS
Hypercholesterolemia	12/35 (34)	24/40 (60)	0.026
Smoker	8/34 (24)	10/40 (25)	NS
Beta-blockers	9/41 (22)	12/41 (29)	NS
Nitrates	7/41 (17)	9/41 (22)	NS
Calcium blockers	3/41 (7)	8/41 (20)	NS
ACE inhibitors	11/41 (27)	16/41 (39)	NS

Data are presented as the mean value ± SD or n/N (%) of patients.
ACE = angiotensin-converting enzyme; DBP = diastolic blood pressure; DM = diabetes mellitus; HR = heart rate; NS = nonsignificant; SBP = systolic blood pressure.

Coronary angiography. Coronary artery disease was excluded during routine coronary angiography, using the Judkin's technique, in 13 patients. Coronary stenoses were quantitated using edge-detection software (Philips, Best, Netherlands); a diameter reduction >50% was considered significant. The interval between DbE and coronary angiography was 4 ± 2 weeks.

Inter-observer and intra-observer variability. Inter-observer and intra-observer variability in the measurement of Sm and Em were evaluated in 16 subjects (8 each from the diabetic and control groups) randomly selected from the 82 subjects. Intra-observer reproducibility of Sm and Em was assessed by one observer at separate times (at least two weeks). To test inter-observer variability, another observer who was unaware of patient identity and the first observer's results analyzed the same patients' data in the same way.

Statistical analysis. All values are expressed as a mean ± SD. The Student *t* test was used to compare the difference between the two groups. Linear regression was used to investigate the correlation between two parametric variables. Data were analyzed using standard statistical software (SPSS, version 11.0, Chicago, Illinois). A p value <0.05 was considered statistically significant.

RESULTS

Clinical characteristics. Table 1 summarizes the clinical characteristics of the two groups, who had comparable mean age, HR, cardiac medications, resting diastolic BP and peak BPs, smoking history, and LV systolic and diastolic function. Diabetic patients showed a greater prevalence of obesity than controls.

Echocardiographic characteristics. Table 2 shows the clinical characteristics of diabetic patients, and Table 3 summarizes the echocardiographic features of the diabetic and control groups. In the diabetic group, basal segment resting Sm and Em were significantly lower than those in controls. Diabetic duration and indexes of diabetic control (glycosylated hemoglobin or blood glucose) were not correlated with resting Sm or Em. There were no significant differences in resting Sm and Em in subgroups of patients with or without complications (e.g., nephropathy, retinopathy, and neuropathy). These parameters did not differ

Table 2. Clinical Characteristics of Diabetic Patients (n = 41)

History of diabetes	
Duration (yrs)	11 ± 10
Type I	5 (12)
Complications of diabetes	
Stroke	2 (5)
Peripheral vascular disease	9 (22)
Renal impairment	7 (17)
Retinopathy	10 (24)
Neuropathy	10 (24)
Blood biochemistry	
HbA_{1C} (%)	7.4 ± 2.0
Glucose (mmol/l)	10.5 ± 4.8
Creatinine (μmol/l)	0.10 ± 0.1
Urea (mmol/l)	8.1 ± 4.1
Lipid profile	
Total cholesterol (mmol/l)	4.9 ± 1.0
LDL cholesterol (mmol/l)	2.4 ± 0.9
HDL cholesterol (mmol/l)	1.3 ± 0.5
TG (mmol/l)	2.1 ± 1.1
Diabetic treatment	
Insulin	10 (24)
Diet therapy	5 (12)
Metformin	11 (27)
Sulfonylureas	18 (44)

Data are presented as the mean value ± SD or number (%) of patients.
HbA_{1C} = glycosylated hemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein; TG = triglycerides.

Table 3. Echocardiographic Characteristics of Each Group

	Control Group (n = 41)	DM Group (n = 41)	p Value
LVEDD (cm)	4.6 ± 0.4	4.6 ± 0.5	NS
IVSD (cm)	1.0 ± 0.2	1.1 ± 0.1	0.008
PWD (cm)	1.0 ± 0.2	1.0 ± 0.1	NS
LVFS (%)	29 ± 4	29 ± 4	NS
LVMI (g/m^2)	92 ± 21	96 ± 21	NS
LVEDV (ml)	86 ± 32	93 ± 23	NS
LVESV (ml)	32 ± 14	37 ± 16	NS
LVEF (%)	63 ± 7	62 ± 5	NS
E (m/s)	0.82 ± 0.23	0.81 ± 0.18	NS
A (m/s)	0.75 ± 0.31	0.82 ± 0.25	NS
E/A ratio	1.20 ± 0.51	1.04 ± 0.33	NS
DT (ms)	233 ± 80	248 ± 52	NS
Resting Sm (cm/s)	4.7 ± 0.9	4.2 ± 0.9	0.012
Resting Em (cm/s)	5.8 ± 1.5	4.2 ± 1.2	<0.001

Data are presented as the mean value ± SD.
A = mitral late peak velocity; DM = diabetes mellitus; DT = mitral valve deceleration time; E = mitral early peak velocity; E/A = ratio of early to late peak diastolic transmitral flow velocity; Em = peak myocardial early velocity; IVSD = inter-ventricular septal dimension; LV = left ventricular; LVEDD = left ventricular end-diastolic dimension; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; LVFS = left ventricular fractional shortening; NS = nonsignificant, PWD = end-diastolic posterior wall thickness; Sm = peak myocardial systolic velocity.

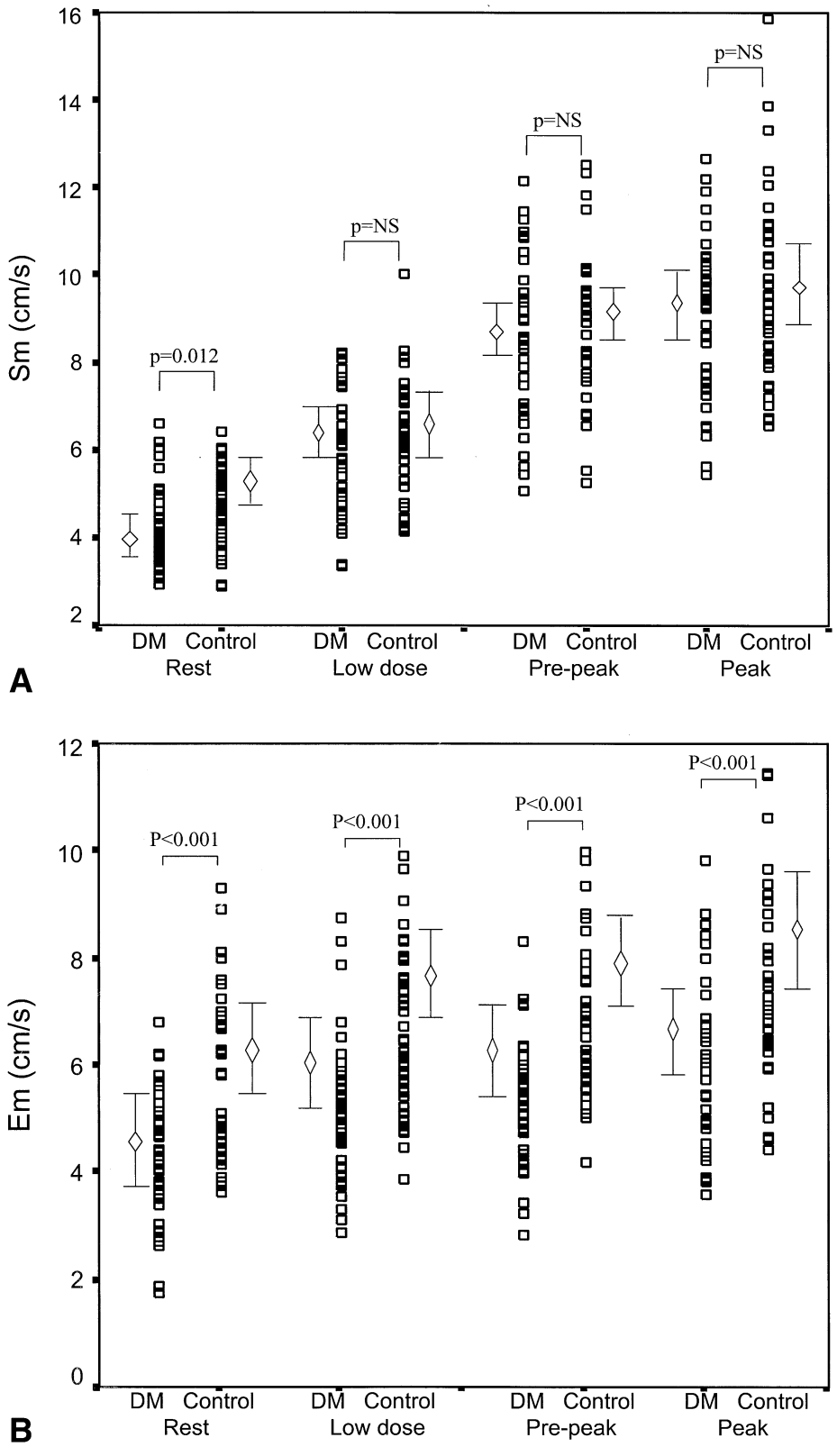

Figure 2. The tissue Doppler imaging-derived myocardial peak systolic velocity (Sm) **(A)** and myocardial peak early diastolic velocity (Em) **(B)** values from rest to peak dobutamine stress in diabetic patients (DM) and control subjects.

according to treatment with and without angiotensin-converting enzyme inhibitors or between patients treated with insulin or oral hypoglycemic drugs.

Sm and Em. Figure 2 shows Sm and Em in diabetic and control groups in relation to different stages of DbE. Both Sm and Em were significantly correlated from the rest to

peak stage. In the diabetic group, Sm was significantly lower than in the control subjects at baseline (4.2 ± 0.9 cm/s vs. 4.7 ± 0.9 cm/s, $p = 0.012$). In a linear model, diabetes ($p = 0.012$) and ejection fraction ($p = 0.042$) were independent predictors of resting Sm. As previously described, Sm showed a progressive increase from resting to peak DbE in both groups. However, Sm at a low dose (6.0 ± 1.3), pre-peak (8.4 ± 1.8), and peak stress (8.9 ± 1.8) in diabetic patients was not significantly different from that in controls (6.3 ± 1.4, 8.9 ± 1.6, and 9.6 ± 2.1 cm/s, respectively). The absolute increase (4.7 ± 1.6 vs. 4.9 ± 1.9 cm/s) and relative increase (115 ± 42% vs. 108 ± 49%) in Sm from resting to peak stage were similar in the diabetic versus the control group, respectively.

Resting Em in the diabetic group was significantly lower than that in the control group (4.2 ± 1.2 vs. 5.8 ± 1.5 cm/s, $p \leq 0.001$). In a linear model, diabetes ($p < 0.001$), hypertension ($p = 0.039$), HR ($p = 0.009$), age ($p < 0.001$), mitral inflow E velocity ($p < 0.001$), and E/A ($p < 0.001$) were associated with resting Em, but only diabetes ($p < 0.001$), E ($p = 0.002$) and E/A ($p < 0.001$) were independent predictors of resting Em.

The Em also showed a progressive increase from resting to peak DbE in both groups. In the diabetic group, the Em ([cm/s] low dose: 5.0 ± 1.4; pre-peak: 5.3 ± 1.1; peak: 5.9 ± 1.5) was significantly lower than that in the control group (low dose: 6.6 ± 1.5; pre-peak: 6.9 ± 1.3; peak: 7.3 ± 1.7; all $p \leq 0.001$). However, the absolute increase (1.7 ± 1.5 vs. 1.6 ± 1.2 cm/s) and relative increase (49 ± 58% vs. 30 ± 26%) in Em from resting to peak dose were also similar in the diabetic versus control groups, respectively.

Inter-observer and intra-observer variabilities. There were no significant differences in Sm and Em between the first measurement (7.2 ± 2.7 and 6.3 ± 1.9 cm/s, respectively) and the second measurement of the same observer (7.4 ± 3.0 cm/s, $r = 0.98$, $p < 0.001$ and 6.4 ± 2.0 cm/s, $r = 0.96$, $p < 0.001$, respectively) or a second observer (6.7 ± 2.8 cm/s, $r = 0.96$, $p < 0.001$ and 6.1 ± 1.9 cm/s, $r = 0.93$, $p < 0.001$, respectively). Mean absolute differences in Sm and Em were 0.4 ± 0.5 cm/s (range 0.0 to 2.3) and 0.4 ± 0.4 cm/s (range 0.0 to 1.6) between the two measurements by the same observer and 0.7 ± 0.6 cm/s (range 0.0 to 2.2) and 0.5 ± 0.5 cm/s (range 0.0 to 2.0) between the two observers.

DISCUSSION

Experimental and clinical evidence has shown that diabetes is associated with LV systolic and diastolic dysfunction. This study shows that sensitive indexes of systolic and diastolic function are abnormal in diabetic patients with a normal ejection fraction and without coronary heart disease and LV hypertrophy. However, the absence of an abnormal response to stress argues against a role for ischemia in the etiology of this dysfunction.

Application of TDI techniques to myocardial assessment. In diabetic patients without overt evidence of heart disease, in whom the ejection fraction is normal at rest, a number of studies have demonstrated abnormal patterns of diastolic inflow, suggesting underlying disturbances of compliance or relaxation (19). Unfortunately, transmitral flow is determined by filling pressure as well as LV relaxation and compliance. Tissue Doppler-derived parameters have the benefit of being less load-dependent and of being sensitive to changes not identified by conventional mitral Doppler inflow indexes (20,21). Moreover, Shan et al. (22) have shown Em to be inversely related to interstitial fibrosis.

Although the ejection fraction is used to assess global LV function, it is very load-dependent, may be influenced by compensatory hyperkinesia, and is an insensitive measure of systolic function. In contrast, measurement of the ventricular long-axis velocities using TDI is thought to provide a more sensitive index of systolic function than LV ejection fraction, as it reflects the subendocardial position of the longitudinal fibers, which are vulnerable to ischemia, LV hypertrophy, and other abnormalities of activation and relaxation (23). The results of this study add diabetes to a number of disorders where TDI has identified subtle abnormalities of systolic base-apex function in patients with normal or mildly impaired LV systolic function (5–7,20).

Causes of subclinical LV dysfunction in diabetes. Regional function is dependent on the number of normally functioning myocytes and the status of the cardiac interstitium. In diabetic subjects, myocytes may be abnormal because of hypertrophy, ischemia, or metabolic disturbances. We believe that hypertrophy is an unlikely explanation, as the selection of patients avoided those with increased LV mass. A reduction of coronary perfusion is possible due to epicardial disease or small-vessel disease, but the presence of normal coronary angiograms, normal dobutamine echocardiograms, and the preservation of systolic reserve (an increment of velocity with dobutamine) all *argue against an ischemic etiology for this resting dysfunction.* This is also supported by previous studies showing no difference in small-vessel pathology and luminal area between diabetic and nondiabetic subjects without significant CAD and with normal LV mass (24) as well as the presence of modestly increased LV end-diastolic pressure, decreased LV compliance, and even a low ejection fraction with diffuse hypokinesia in diabetic patients after exclusions of CAD by coronary angiography and small-vessel disease by atrial pacing (3). A metabolic disturbance associated with reduced force generation cannot be excluded by this study, but it seems less likely in the absence of an apparent relationship with diabetic control.

As changes were detected in the absence of hypertrophy and ischemia and were not altered by stress, the findings of this study would be consistent with myocardial fibrosis being the main cause of the myocardial functional changes

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(25). This is because the interstitium has a more important role—relative to myocyte function—at rest than it does at stress, when contractile behavior increases several-fold but the elastic component remains the same. An alternate explanation is that the contractile response is preserved because diabetic neuropathy and adrenoreceptor supersensitivity may play a role in provoking a blunted inotropic response to dobutamine. Indeed, this interpretation is consistent with the hypothesis that diabetic heart disease is related to defects in calcium transportation, myocardial contractile protein collagen formation, and fatty acid metabolism, leading to myocyte hypertrophy and myocardial fibrosis. Interstitial collagen accumulation has been shown to be associated with enhanced diastolic stiffness in a dog model of diabetes (26), and likewise, the extent and progressive increase in these abnormalities have been thought to contribute to measurable diastolic dysfunction of diabetic patients (27). The resulting disturbances in diastolic function may explain the clinical presentation of heart failure symptoms in diabetic patients.

Study limitations. Exclusion of an ischemic contribution was based on a normal dobutamine echocardiogram, together with a normal coronary angiogram, in 13 patients. The possibility of false-negative studies cannot be excluded, as more uniform application of invasive techniques (e.g., coronary angiography and flow reserve) would not be ethically applicable in these asymptomatic patients, and positron emission tomography was not available. However, the lack of coronary disease was supported by the lack of a decrement of velocity with dobutamine in the diabetic group.

The control group was comprised of a nondiabetic population considered to have a low probability of coronary disease on clinical grounds and having a normal dobutamine echocardiogram. It is possible that their clinical status may have affected the control group results, but we consider this unlikely because this group was well matched with the diabetic subjects (Tables 1 and 3).

Doppler techniques are also angle-dependent and may be influenced by the translational movement of the heart during dobutamine stress. However, we excluded segments with an angle $>20^{\circ}$ between the Doppler beam and the longitudinal walls, or a change of image orientation $>20^{\circ}$ among the stages of dobutamine stress, which should minimize this source of error.

Conclusions. This study demonstrates that abnormalities of systolic and diastolic function are prevalent in diabetic patients, despite the absence of overt systolic dysfunction or CAD and LV hypertrophy. Diabetic patients do not show an abnormal response to stress, suggesting that small-vessel disease may not play a causative role in early diabetic cardiomyopathy. Quantitative assessment of Sm and Em using TDI techniques offers a feasible approach to the assessment of subclinical LV function and may allow the early detection of diabetic heart disease.

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